Disease-Specific Diagnosis of Coinfecting Tickborne Zoonoses: Babesiosis, Human Granulocytic Ehrlichiosis, and Lyme Disease

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To determine whether a unique group of clinical and laboratory manifestations characterize certain major deer tick–transmitted human pathogens in North America, we compared the symptoms, short-term complications, and laboratory test results of New England residents who became ill due to ⩾1 of these pathogens. Patients completed a uniformly structured questionnaire and submitted blood samples for serologic and polymerase chain reaction (PCR) testing after developing symptoms of Lyme disease, human babesiosis, or human granulocytic ehrlichiosis (HGE). Complete blood count with thin blood smear, PCR, and immunoglobulin M antibody tests helped differentiate the acute manifestations of these diseases. Physicians should consider use of tests designed to diagnose babesiosis and HGE in patients with Lyme disease who experience a prolonged flulike illness that fails to respond to appropriate antiborrelial therapy.

Lyme disease, babesiosis, and human granulocytic ehrlichiosis (HGE) cause a diverse array of symptoms in residents of endemic sites in the northeastern and northern Midwestern United States [1–9]. The respective zoonotic pathogens are maintained in cycles comprised of the vector ticks *(Ixodes scapularis,* also known as *Ixodes dammini)* and reservoir mice *(Peromyscus leucopus).* In vector ticks, infection with one of these agents frequently accompanies infection by the others. Approximately 16,000 cases of Lyme disease are reported to the US Centers for Disease Control and Prevention (CDC) each year [10]. Antibabesial antibody is present in the sera of approximately one-tenth of Connecticut and Rhode Island residents whose sera also react with antiborrelial antibody [11, 12]. As many as two-thirds of New York residents with *Borrelia*-reactive sera also have *Babesia*-reactive sera [13]. Antiehrlichial antibody is present in approximately one-tenth to one-fifth of Connecticut residents whose sera contain antiborrelial antibody [14, 15]. Numerous residents of the United States experience infection with one or another of these *Ixodes*-borne pathogens, alone or in combination.

Because these diverse *Ixodes*-transmitted infections frequently are cotransmitted, the spectrum of acute disease may be highly variable. Previous descriptions of the clinical manifestations of these diseases were recorded before the likelihood of coinfection was widely recognized and before many current diagnostic tests

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became available. Only 2 such systematic analyses of the clinical course of acute infection with 2 of these agents in North America are now available [12, 16]. The first study concluded that 11% of patients with Lyme disease in southern New England also experience concurrent babesiosis, and that patients who are coinfected with the causative agents appear to experience more-diverse and longer-lasting symptoms than do those infected with the agent of Lyme disease alone [12]. The second study found that 13% of patients with Lyme disease in Wisconsin also experience concurrent HGE and that the clinical spectrum of HGE overlaps that of Lyme disease [16]. We lack information concerning the diversity and duration of acute symptoms due to each of the 3 known *Ixodes*-transmitted infections, and we cannot distinguish single infection from concurrent infection on the basis of clinical manifestations of disease.

It may be possible to devise a system for identifying patients concurrently infected with the Lyme disease spirochete and with the agents of babesiosis or HGE. To this end, we conducted a prospective longitudinal study designed to determine whether a unique group of clinical and laboratory manifestations of disease might characterize patients coinfected with these various pathogens.

PATIENTS AND METHODS

Case finding and clinical analyses protocol. Study physicians attempted to enroll any patient who experienced an erythema migrans rash or flulike illness suggestive of Lyme disease, babesiosis, or HGE that occurred during the months of May through September 1997–2000 among the residents of Block Island, RI, Nantucket, MA, and southeastern Connecticut. Study physicians at all sites followed a uniform study protocol. After obtaining written informed consent, the physicians obtained a medical history and performed a physical examination. At the time of presentation, each patient completed a standardized questionnaire. A medical history was obtained again within the next month and repeatedly until the patient had become asymptomatic. We sought evidence of severity of disease by recording the frequency of each of the symptoms and signs that were evident at presentation or were reported by the patient. A sample of blood was obtained during the acute and convalescent stages of their illness for pathogen-specific serologic and PCR assays for *Borrelia burgdorferi, Babesia microti,* and the agent of HGE. Appropriate informed consent was obtained, and clinical research was conducted in accordance with guidelines for human experimentation, as specified by the internal review boards at Connecticut Children's Medical Center (Hartford) and the Harvard School of Public Health (Boston).

Case definitions. The criteria that we used for the diagnosis of Lyme disease and babesiosis are described elsewhere [12]. Diagnosis of acute HGE required the presence of symptoms consistent with HGE and laboratory evidence of HGE, including anti-HGE antibody seroconversion, with or without identification of ehrlichia (morulae) on thin blood smear or amplification of *Ehrlichia equi* DNA in a blood sample by a specific PCR test.

Laboratory assays. Piroplasm merozoites or ehrlichia (morulae) were identified microscopically in Giemsa-stained films of EDTA-anticoagulated blood [17]. At least 100 fields (magnification, ×400) were examined before the sample was declared to be free of piroplasms or morulae. Serologic evidence of exposure to the Lyme disease spirochete was detected with ELISA by use of an assay described elsewhere [11]. All borderline or reactive serum samples were further characterized by immunoblot assay [18]. Specimens were considered to be positive on the basis of the criteria of the CDC and the Association of State and Territorial Public Health Laboratory Directors [19].

Babesial infection was diagnosed serologically by an indirect immunofluorescence assay, as described elsewhere [11]. A specimen was considered to have a positive response if it reacted at a dilution of 1:64 or greater. HGE was diagnosed serologically by ELISA, as described elsewhere [20]. A standardized recombinant HGE-44 suspension was used as the antigen. DNA of the agents of Lyme disease, babesiosis, and HGE was detected by means of pathogen-specific PCR assays, as described elsewhere [21–23]. The gene targets included a 294-bp portion of the *B. burgdorferi ospA* gene, a 238-bp portion of the *B. microti* nuclear small subunit ribosomal gene, and a 247-bp portion of the *Ehrlichia phagocytophila/E. equi* nuclear small subunit ribosomal gene.

Data analysis. A χ^2 test (or Fisher's exact test, when expected cell frequencies were <5) was used to examine differences in the occurrence of symptoms between groups of patients. Differences in the symptom index were evaluated using the Kruskal-Wallis test. Differences in disease duration were assessed using the log-rank test.

RESULTS

Epidemiologic features of infection. Of the 310 residents of Block Island, Nantucket, and southeastern Connecticut who were enrolled in our study because they had suspected tick-borne illness, clinical manifestations were recorded for the 192 subjects with confirmed infection. Some of these 192 subjects experienced Lyme disease, babesiosis, or HGE alone; others were coinfected with ≥2 pathogens (table 1). Coinfection accounted for 75 (39%) of the cases and was mainly due to concurrent infections with the agents of Lyme disease and babesiosis. Among the Block Island cohort of patients infected with the Lyme disease spirochete, 17 (22%) were

Table 1. Characteristics of study patients enrolled in a study assessing the incidence of Lyme disease, babesiosis, and human granulocytic ehrlichiosis (HGE) in patients recruited from Block Island, Rhode Island (BI), Nantucket, Massachusetts (N), and southeastern Connecticut (CT).

Disease	No. of patients, by location				Female patients, %	Age, mean years	No. of immune-impaired patients	Time from disease onset to receipt of therapy, mean days (range)
	BI	N	CT	All				
Single								
Lyme disease	57	25	7	89	45	44	1	6.4 (1–30)
Babesiosis	2	20	3	25	36	59	2	9.8 (4–42)
HGE	2	0	1	3	67	34	0	6.0 (2–12)
Concurrent								
Lyme disease and babesiosis	16	37	8	61	44	47	1	6.9 (1–30)
Lyme disease and HGE	2	2	3	7	57	39	0	9.3 (1–20)
Lyme disease, babesiosis, and HGE	1	1	2	4	100	60	1	15 (4–29)
Babesiosis and HGE	0	2	1	3	33	37	0	13 (3–22)
All	80	87	25	192	45	46	5	

concurrently infected with the babesial piroplasm and 3 (4%) were concurrently infected with the HGE bacterium. Only 10 (17%) of the 59 subjects who presented with a flulike illness without rash were found to be infected with a tickborne pathogen on Block Island, where no laboratory screening of participants was available before their enrollment in the study. Although most patients with flulike illness were not infected with a tickborne pathogen, Lyme disease and babesiosis (both alone and in combination) were commonly diagnosed at each of our study sites.

Patient characteristics. Patients at all of the study sites who experienced babesiosis alone were older than those who experienced Lyme disease alone, HGE alone, or concurrent babesiosis and Lyme disease (table 1). No other significant differences in age characterized our study groups. The sex distribution of patients infected with these various tickborne pathogens was similar. Only 5 of the 192 patients had immunosuppression, and the proportions of such patients in the single-infection and coinfection groups were similar. All patients who experienced Lyme disease received appropriate antimicrobial therapy consisting of a ≥2 week regimen of amoxicillin or doxycycline. Because symptoms had resolved or improved by the time concurrent babesiosis or HGE was diagnosed, therapy was not administered to 38 (58%) of the patients with Lyme disease plus babesiosis and 6 (57%) of the patients with Lyme disease plus HGE. The time from onset of illness until initiation of antimicrobial therapy was similar among the various patients. The distributions of age, sex, immunosuppression status, and antimicrobial therapy in our various samples of patients generally appear to be similar.

Clinical manifestations. We determined whether specific symptoms or signs might be used to discriminate between patients experiencing episodes of disease attributed solely to babesiosis, HGE, or Lyme disease. Virtually all of our patients experienced either an erythema migrans rash alone, flulike symptoms (e.g., fever, chills, sweats, headache, fatigue, arthralgia, myalgia, cough, conjunctivitis, sore throat, anorexia, nausea, and vomiting) without a rash, or an erythema migrans rash with flulike symptoms. An erythema migrans rash, with or without flulike symptoms, generally was present (90%) in patients with Lyme disease and served as the basis for diagnosis in these individuals. In contrast, none of the patients who received diagnoses of babesiosis or HGE alone presented with a rash. Flulike symptoms without rash were observed in only 10% of patients with Lyme disease alone but in all patients with babesiosis or HGE alone. Erythema migrans serves as a useful clinical parameter for differentiating patients with Lyme disease alone from those with babesiosis or HGE, and flulike symptoms without rash are characteristic of babesiosis and HGE.

Next, we determined whether specific symptoms or signs might be used to discriminate between patients with episodes of Lyme disease alone and those with Lyme disease accompanied by babesiosis, HGE, or both. Most patients with Lyme disease, either alone or in combination with babesiosis or HGE, presented both with an erythema migrans rash and flulike symptoms (table 2). A higher percentage of patients with concurrent Lyme disease and babesiosis or HGE experienced flulike symptoms than did those with Lyme disease alone (table 2). An erythema migrans rash by itself is more suggestive of Lyme disease alone than it is of Lyme disease with a concurrent disease, whereas flulike symptoms without an erythema migrans rash are more suggestive of Lyme disease with a concurrent disease than of Lyme disease alone.

We next determined whether any 1 or a combination of 17 clinical manifestations of illness might serve to distinguish between patients with Lyme disease alone, patients with babesiosis or HGE alone, and patients with Lyme disease and

Table 2. Erythema migrans rash and flulike symptoms among patients recruited from Block Island, Rhode Island, Nantucket, Massachusetts, and southeastern Connecticut in a study assessing the clinical manifestations of Lyme disease, babesiosis, and human granulocytic ehrlichiosis (HGE).

Disease	No. of patients	Clinical signs, % of patients		
		Erythema migrans	Flulike symptoms	Both
Single				
Lyme disease	89	11	10	79
Babesiosis	25	0	100	0
HGE	3	0	100	0
Concurrent				
Lyme disease and babesiosis	61	2	21	77
Lyme disease and HGE	7	0	14	86
Lyme disease, babesiosis, and HGE	4	0	75	25
Babesiosis and HGE	3	0	100	0

concurrent babesiosis or HGE. The combination of fever, chills, and headache was noted in approximately one-half of the patients with Lyme disease coinfection (32 [44%]), compared with approximately one-tenth (12 [13%]) of those with Lyme disease alone. Patients with Lyme disease alone reported fewer and more-transient symptoms than did those infected with the agents of babesiosis or HGE or those with Lyme disease and concurrent babesiosis or HGE (table 3). The combination of fever, chills, and headache in patients with Lyme disease suggests that these patients are concurrently infected with the agents of babesiosis, HGE, or both. Concurrent infection tends to increase the diversity and duration of symptoms attributed to Lyme disease.

Dissemination of infection. We next determined whether concurrent babesial or ehrlichial infection enhanced the dissemination of the Lyme disease spirochete into skin, joint, nerve, or heart tissue, and whether such an event might serve as a diagnostic indicator of concurrent infection. Spirochetal dissemination into skin, as assessed by the development of disseminated erythema migrans rash, was observed in 13 (15%) of the patients with Lyme disease alone and in 13 (18%) of the patients with Lyme disease and concurrent babesial or ehrlichial infection. Joints became swollen in 8 (9%) of the patients with Lyme disease alone and 6 (8%) of the patients with Lyme disease and concurrent infection. Only 1 patient (1%) with Lyme disease alone received a physician's diagnosis of arthritis, compared with none of the patients who had Lyme disease and concurrent infection. A physician's diagnosis of acute neurologic abnormalities (e.g., Bells palsy or meningitis) was made for 2 (2%) of the subjects with Lyme disease alone and 2 (3%) of those with Lyme disease and concurrent infection. None of our patients had acute cardiac complications diagnosed. In sum, concurrent babesiosis or HGE does not appear to increase the probability of acute dissemination of the Lyme disease spirochete into blood, skin, joint, nerve, or heart tissue.

Laboratory tests. We then compared the utility of the complete blood count (CBC), blood smear, PCR, and IgM antibody tests for early diagnosis of infection. CBC results were available for patients with Lyme disease alone, patients with babesiosis alone, and patients with concurrent Lyme disease, babesiosis, and HGE (table 4). Although the findings of CBCs for patients with Lyme disease alone were normal, patients with Lyme disease and concurrent babesiosis had anemia and thrombocytopenia, and patients with Lyme disease and HGE had leukopenia. Anemia and thrombocytopenia characterize patients with babesiosis alone or accompanied by concurrent HGE; leukopenia may occur in patients with Lyme disease and HGE.

The utility of specific laboratory test results as a basis for definitive diagnosis was evaluated. The babesial pathogens themselves were detected microscopically in 31 patients (33%) with babesiosis, including 17 (67%) of those with babesiosis alone, but not in subjects with HGE or Lyme disease. Specific amplifiable DNA was detectable in 60 (71%) of all patients with babesiosis, 7 (41%) of those with HGE, and 1 (4%) of those with Lyme disease who had PCR performed. IgM antibody was detected in 73 (78%) of the subjects with babesiosis, 14 (82%) of those with HGE, and 40 (47%) of those with Lyme disease who had IgM performed. Babesiosis frequently can be diagnosed microscopically, babesiosis and HGE can be diagnosed by PCR, and all 3 diseases can be diagnosed by serologic testing.

DISCUSSION

Acute Lyme disease is readily diagnosed when the pathognomonic erythema migrans rash is present [4–6]. Human babesiosis and HGE, on the other hand, lack such a prominent diagnostic sign; they produce nonspecific, flulike symptoms that tend to be confused with the symptoms of a summer viral illness [2, 3, 7–12, 24]. Flulike symptoms also are common in patients with Lyme disease, but they are present without an erythema migrans rash in only ~10% of cases [25–28]. Indeed, the presence of flulike symptoms without rash—and especially the combination of fever, chills, and headache—in patients with Lyme disease is suggestive of concurrent babesiosis or HGE. In addition, diverse and persistent symptoms are more characteristic of patients with Lyme disease and concurrent babesiosis or HGE than they are of patients with Lyme disease alone. Physicians who treat patients with Lyme disease should consider performing laboratory tests for babesiosis and HGE for persons who have a prolonged flulike illness that fails to respond to appropriate antiborrelial ther-

Table 3. Clinical manifestations and duration of illness in patients infected with the agents of Lyme disease alone *(Borrelia burgdorferi)*, babesiosis alone *(Babesia microti)*, ehrlichiosis alone (the agent of human granulocytic ehrlichiosis [HGE]), Lyme disease and babesiosis, or Lyme disease and HGE.

Manifestation or characteristic	Percentage of patients, by agent of infection					Significant *P* values for infection with *B. burgdorferi* vs. concurrent infection	
	B. burgdorferi (n = 89)	*B. microti* (n = 26)	Agent of HGE (n = 3)	*B. burgdorferi* and *B. microti* (n = 64)	*B. burgdorferi* and the agent of HGE (n = 7)	*B. burgdorferi* and *B. microti*	*B. burgdorferi* and the agent of HGE
Chills	21	81	33	50	71	<.001	.01
Sweats	22	96	67	42	71	.02	.01
Headache	45	81	100	69	86	.005	.05
Fatigue	37	92	100	77	71	.02	—
Fever	40	88	100	59	71	.03	—
Nausea	14	38	33	34	14	.008	—
Arthralgia	46	46	67	47	100	—	.01
Sore throat	15	31	0	19	57	—	.02
Myalgia	49	85	33	58	57	—	—
Anorexia	29	65	67	45	57	—	—
Erythema migrans	90	0	0	80	86	—	—
Emotional lability	12	50	67	23	43	—	—
Neck stiffness	42	42	0	45	57	—	—
Cough	11	46	33	22	14	—	—
Joint swelling	10	12	0	8	14	—	—
Vomiting	2	19	0	11	0	—	—
Conjunctivitis	4	12	0	5	0	—	—
Mean number of symptoms ± SD	5.3 ± 3	8.8 ± 3	7.3 ± 2	7.0 ± 3	9.4 ± 1	<.001	<.001
Duration of symptoms, mean weeks ± SD	3.9 ± 4	9.7 ± 8	1.0 ± 0	5.5 ± 5	11.0 ± 10	<.055	<.001

Table 4. Mean complete blood count values for patients with Lyme disease, babesiosis, and/or human granulocytic ehrlichiosis (HGE).

Disease	No. of patients	Mean blood count value				
		Hematocrit, %	Hemoglobin, g/dL	WBCs, $\times 10^9$/L	Polymorphonuclear leukocytes, %	Platelets, $\times 10^9$/L
Single						
Lyme disease	7	44.5	14.9	5.8	65.7	201
Babesiosis	17	36.4	12.2	4.7	51.3	79
Concurrent						
Lyme disease and babesiosis	9	39	13.1	4.9	61.6	114
Lyme disease and HGE	2	40.8	14.0	4.3	58.5	232
Lyme disease, babesiosis, and HGE	3	34.3	11.8	6.4	50.6	126
Babesiosis and HGE	3	37.7	12.8	5.0	40.9	140
Lyme disease and any other	21	40.3	13.5	5.3	61.6	153
Babesiosis and any other	32	38.0	12.9	5.0	51.8	110
HGE and any other	8	37.7	12.8	5.0	40.9	140
Normal range	—	42–52	14–18	4.8–10.8	40–70	150–400

apy, especially if the combination of fever, chills, and headache is present.

A CBC that includes a blood smear is the best initial laboratory test for patients thought to have babesial or ehrlichial infection, including those with suspected Lyme disease and babesial or ehrlichial coinfection. Such screening tests are useful, because only a small percentage of patients with summertime flulike illness in areas of endemicity are infected with the agents of babesiosis or HGE. In our study, 17% of Block Island subjects who experienced flulike symptoms were infected with ⩾1 tickborne pathogen. We confirmed previously described observations that anemia and thrombocytopenia were associated with babesiosis and that neutropenia and thrombocytopenia were associated with HGE [24, 29, 30]. No such hematologic abnormalities were observed in our patients who experienced Lyme disease alone.

Giemsa staining should be performed on the thin blood smear that is prepared for the CBC, and the stained smear should be examined for babesial parasites and ehrlichial morulae. Testing for IgM antibody may be useful for the diagnosis of babesiosis or HGE during the acute phase of the illness [9, 31]. The use of PCR to detect specific amplifiable DNA in blood is advisable in suspected cases of babesiosis, because parasites may be difficult to detect on a thin blood smear early in the course of babesial infection [22, 32]. Microscopic study may detect babesial parasites in more than one-third of patients with babesiosis, and babesial parasites may be detected in an additional one-third by means of PCR. Specific diagnostic testing for coinfecting babesial and HGE pathogens can be rapid, sensitive, and specific, but the number of laboratories that currently offer this service is limited. Therefore, patients thought to be experiencing tickborne infection should be screened by means of CBC and examination of a Giemsa-stained thin blood smear, followed by specific IgM and IgG antibody and PCR testing.

The effect of concurrent infection with the agents of babesiosis and HGE on the clinical outcome of Lyme disease is paradoxical. Although the diversity and duration of symptoms reported by patients coinfected by the agents of Lyme disease and babesiosis or HGE exceeds that for patients with Lyme disease alone, the frequencies of disseminated blood, skin, joint, cardiac, and neurologic disease and of hospital admission appear to be similar. Our observation that coinfected patients with Lyme disease experience more flulike symptoms than do those with Lyme disease alone confirms our previous observation and extends this conclusion to include concurrent Lyme disease and HGE [12]. Previous reports of concurrent human Lyme disease and babesiosis or HGE suggest that coinfection may exacerbate illness [23, 33–35]. In contrast, we found no evidence that *Babesia* species or HGE enhanced the dissemination of *B. burgdorferi* into the joint, nerve, or heart tissue of our patients. A similar lack of long-term musculoskeletal and neurologic effects in patients infected with the agents of Lyme disease and babesiosis has been noted elsewhere [36], although this observation is difficult to interpret because infection in that study population may have been sequential rather than concurrent. Previous animal studies have provided mixed results with regard to the effect of coinfection on disease dissemination [37–39]. Further development of animal models to study the coinfecting agents of Lyme disease, babesiosis, and HGE would help to elucidate the immunologic and pathogenic mechanisms that occur after concurrent tickborne infection. In addition, a carefully de-

signed prospective human study of the short- and long-term complications of Lyme disease and concurrent babesiosis and HGE is needed.

Lyme disease, babesiosis, and HGE impose a health burden on many communities in the northeastern and northern Midwest of the United States. Concurrent infection by more than 1 of these tickborne pathogens is common [12–16]. Physicians practicing in areas where deer tickborne infections are endemic should become familiar with the infections' diverse clinical manifestations so that they can provide optimal diagnosis and appropriate treatment.

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